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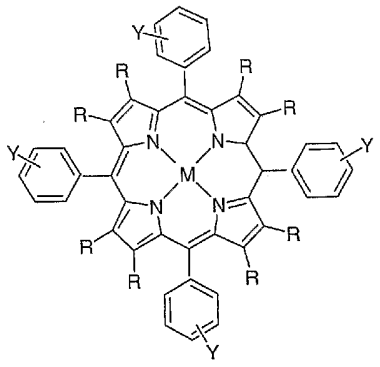
(54) Title: PROCESS FOR THE PREPARATION OF A SUBSTITUTED PORPHYRIN



(I)

(57) Abstract: Processes are disclosed for the preparation of a compound having the formula: (I) and intermediate compounds wherein M is a single-photon-emission tomography imageable radiometal and/or a paramagnetic metal, R is hydrogen or a halogen provided that at least one R is halogen and Y is selected from ortho, meta or para $O(CH_2)_nC_2HB_9H_{10}$ or $O(CH_2)_nC_2HB_{10}H_{10}$ wherein n is 0 or an integer from 1 to 20 and $O(CH_2)_nC_2HB_9H_{10}$ is nido ortho-, meta- or para- carborane and $O(CH_2)_nC_2HB_{10}H_{10}$ is ortho-, meta- or para-carborane.

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Process for the Preparation of a Substituted Porphyrin

The present invention relates to a process for the production of a porphyrin of formula (I) and further to a process for the production of an intermediate compound such as compounds of formula (II).

Radiotherapy, although widely used in the management and the treatment of early to advanced stage cancers, has many drawbacks including normal tissue damage and burdensome treatment schedules (up to 6 weeks). Clinical radiotherapy and chemotherapy deliver survival rates that remain inadequate and in some instances totally unacceptable. However, where there is no alternative treatment, which is the case for the vast majority of cancer patients, the use of radiotherapeutic modalities prevails. It is projected that current research efforts will improve the delivery and the outcome of radiotherapy by only 10% over the next 10 years. That is, an increase from 30% to 33% cure rate, with the remaining balance of treatment achieving 70% palliation. A major challenge is to significantly improve this cure rate without compromising normal tissue tolerance. Conservative estimates suggest that over 100,000 patients are treated per day worldwide with conventional radiotherapy and over 5,000 new patients per day arrive into the treatment modality. There is clearly a need to improve the conventional radiotherapy methodology to provide improved cure rates.

One approach to improving cure rates is X-ray activated-drug therapy or photo activated drug therapy (PAT). In this method, an activatable drug is administered to the patient, and the drug is preferentially localised to tumour tissue. This approach may be combined with a number of standard radiotherapy techniques.

X-ray activated-drug therapy (PAT) is capable of replacing conventional radiotherapy for the treatment of cancer. Translation of x-ray activated-drug therapy into the clinic has the potential to deliver staggering cure rates of 85%, up from 30 % with conventional radiotherapy.

Radiotherapy may be given using large X-ray machines. Occasionally gamma rays or electrons may be used. The activatable drugs can be activated using X-rays (as well as ionizing radiation such as gamma rays, electrons, protons, neutrons) that are used in conventional radiotherapy and its variants such as confocal radiotherapy, intensity modulated radiotherapy (IMRT), invasive internal radiotherapy and brachytherapy.

External X-rays are targeted by way of masks (contoured to the shape of the tumour) and beamed in from the outside. Single or multiple x-ray beams at different angles may be used to maximise the x-ray dose to tumour and concurrently minimise the x-ray dose to normal tissue.

Invasive internal radiotherapy involves the introduction of radioactive tubes into the tumour to give a very intense x-ray dose. A number of tumours can be treated in this way, in particular cancer of the cervix, breast and skin.

In brachytherapy, radioactive "seeds" are seriotactically placed within a tumour mass. The radioactive source is generally one of the following: Radium-226, Caesium-137, Cobalt-60, Iridium-192, Gold -198, Strontium-90, Yttrium-90. Other radionuclides suitable for unsealed use are Iodine-131, Phosphorous-32, Yttrium-90.

IMRT is a recent development which uses three dimensional data derived from magnetic resonance imaging (MRI), positron emission tomography (PET),

single-photon-emission tomography (SPECT) and computed tomography (CT)-scans to deliver very precisely x-rays to the target. A pencil beam of x-rays is scanned over the tumour. The beam intensity and the duration (dwell-time) at any one point is varied to dump a maximum of x-ray energy for maximum cell kill. Total X-ray doses over 90-100Gy are now being delivered and are proving to be highly successful.

However, IMRT is data hungry and requires information on the exact dimensions of a tumour and its spread, and small movements of the tumour (0.1mm-1mm) that arise from breathing and the heart beat result in less than optimal x-ray dose delivery to guerrilla cells at the edges of the tumour. Such cells escape treatment and can result in tumour recurrence. A real-time feedback to compensate for tumour movement would assist in this method.

Once a patient is diagnosed with cancer and a decision has been taken to treat the cancer with radiotherapy, patients undergo treatment planning and patient specific X-ray dose calculations generated from the exact location of the tumour, tumour spread and dimensions. Treatment planning information is derived from conventional diagnostic imaging techniques such as MRI, PET, SPECT as well X-ray images and CT scans. Careful planning is necessary to ensure that the treatment area and field includes all of the cancer and avoids vital organs (e.g. heart, spinal cord, gut). Improved methods of imagining tumours are required to assist in such planning.

Porphyrins have been applied in the prior art to various radiation type therapies including boron neutron capture therapy (BNCT) and photodynamic therapy (PDT). Porphyrins are known to have a high affinity for neoblastic tissues in mammals, including man (see, for example, Solloway et al, Chem Rev (1998), 98, 1515-1562, US 5,877,165; British Journal of Radiology (1998), 71, 773-

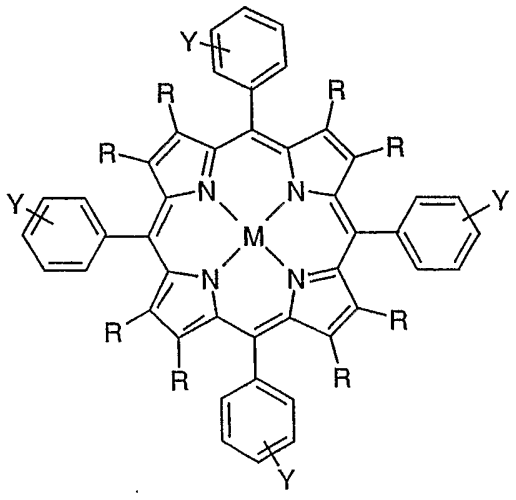
781; Journal of Neuro-Oncology (2001), 52, 111-117; and International Journal of Cancer (1996), 68, 114-119).

Of particular interest has been the category of porphyrins including synthetic tetraphenyl porphyrins (TPP) derivatives including CuTCPH and NiTCPH. These porphyrin rings, existing as chelating agents for nickel and copper atoms, exhibit very favourable localization to tumor tissue in preference to normal tissue or blood. For example, in US 5,877,165 a tumor colon blood ratio of 16:1 is described.

There is a need for further and improved porphyrins for use in therapeutic and diagnostic methods. There is also a need for improved methods of manufacturing such porphyrins. The invention addresses these and other problems.

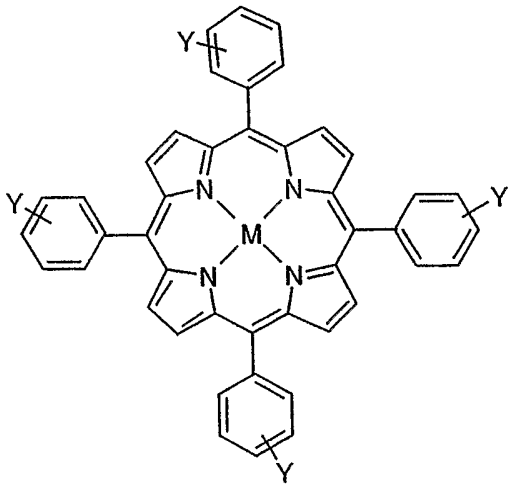
Summary of the Invention

Accordingly, in a first aspect, the invention provides a process for the preparation of a compound having the formula I:



I

wherein M is a single-photon-emission tomography imageable radiometal and/or a paramagnetic metal, R is hydrogen or a halogen provided that at least one R is halogen and Y is selected from ortho, meta or para $O(CH_2)_nC_2HB_9H_{10}$ or $O(CH_2)_nC_2HB_{10}H_{10}$ wherein n is 0 or an integer from 1 to 20 and $O(CH_2)_nC_2HB_9H_{10}$ is nido ortho-, meta- or para-carborane and $O(CH_2)_nC_2HB_{10}H_{10}$ is ortho-, meta- or para-carborane, said process comprising halogenating a compound having the formula III



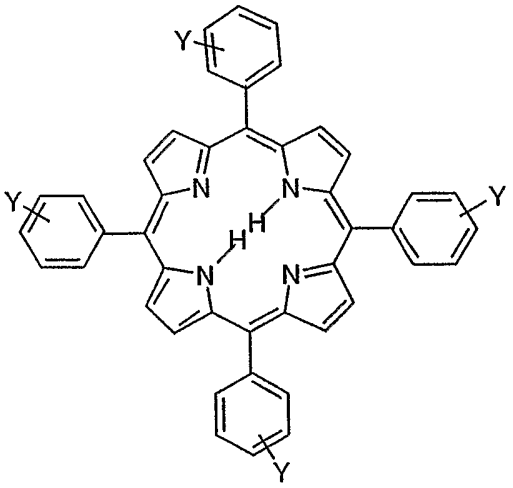
III

wherein Y and M are as defined for the compound of formula I.

The compound of formula I produced by the process of the first aspect contains eight R groups. For the purposes of the invention, each R group is preferably halogen, more preferably each R group is bromide. Y is preferably selected from meta $O\text{-}(CH_2)_n\text{-}C_2HB_9H_{10}$ or meta $O\text{-}(CH_2)_n\text{-}C_2HB_{10}H_{10}$ wherein n is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10. M is preferably a transition metal or a lanthanide metal.

In a particular feature of the first aspect of the invention, the process is preferably is a process for the formation of a compound of formula I wherein M is Cu, each R is bromide and Y is meta O-CH_2-$C_2HB_{10}H_{10}$.

The second aspect of the invention provides a process for the production of a compound of formula (III) as defined above said process comprising combining a compound having the formula II wherein Y is as defined for the compound of formula I;



II

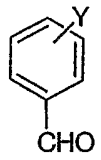
with the acetate of the metal M

The third aspect of the invention provides a process for the production of a compound of formula I from a compound of formula II comprising combining a compound of formula II with a metal acetate to form a compound of formula III *in situ*, and then combining said *in situ* generated compound of formula III with a halogenating agent to form a compound of formula I. It will be appreciated that this one-pot synthesis allows the generation of a compound of formula III *in situ* and avoids the needs for isolation and purification of this intermediate compound.

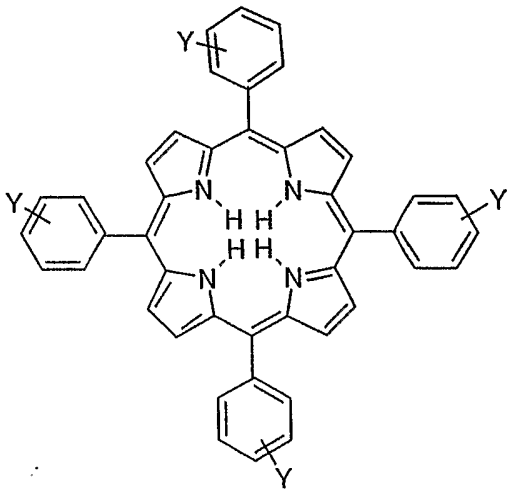
For the purposes of this aspect of the invention, the compound of formula II is preferably combined with the metal acetate in dichloromethane. More preferably, the metal acetate is copper acetate. Halogenation of the *in situ* generated compound of formula III is preferably carried out with bromine. Halogenation preferably occurs in an aliphatic alcohol having from 1 to 6 carbon atoms, more preferably methanol.

The fourth aspect of the invention is directed to a process for the preparation of a compound having the formula II as defined above said process comprising

a) combining an aldehyde having the formula



with pyrrole in the presence of a Lewis acid catalyst to form a compound having the formula IV



IV

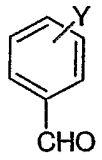
and;

b) oxidising the compound having the formula IV by the addition of from 0.01 to 2 molar equivalents 2,3-dicyanobenzoquinone based on the aldehyde.

The invention further relates to a process of producing a compound having the formula IV as set out above, said process comprising the process set out in step a) above. The invention further relates to a process for producing a compound of formula II from a compound of formula V via the process set out in step b) above.

The fifth aspect of the invention is directed to a process for the preparation of a compound having the formula I as defined above said process comprising

a) combining an aldehyde having the formula



with pyrrole in the presence of a Lewis acid catalyst to form a compound having the formula IV as defined above;

oxidising the compound having the formula IV by the addition of from 0.01 to 2 molar equivalents 2,3 dichloro-5,6 dicyanobenzoquinone based on the aldehyde to form a compound having the formula II as defined above;

c) combining a compound having the formula II with the acetate of the metal M to form a compound having the formula III as defined above; and,

d) combining the compound having the formula III with a halogenating agent to form a compound having the formula I.

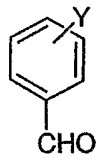
For the purposes of this aspect of the invention, the compound of formula II is preferably combined with the acetate of the metal M in a mixture of dichloromethane and methanol. Alternatively, the compound of formula II is

preferably combined with the acetate of the metal M in dichloromethane. The reaction of the compound of formula II with the metal acetate preferably occurs at ambient temperature.

The halogenation preferably occurs in a mixed solvent solution, preferably a chlorinated solvent or a mixture of chlorinated solvents said chlorinated solvent being selected from trichloromethane, carbon tetrachloride and/or dichloromethane, more preferably dichloromethane. Alternatively, the halogenation is preferably carried out in an aliphatic alcohol having from 1 to 6 carbon atoms, preferably methanol. The halogenation preferably occurs at ambient temperature,

The sixth aspect of the invention is directed to a further process for the preparation of a compound having the formula I as defined above said process comprising

a) combining an aldehyde having the formula



with pyrrole in the presence of a Lewis acid catalyst to form a compound having the formula IV as defined above;

oxidising the compound having the formula IV by the addition of from 0.01 to 2 molar equivalents 2,3 dichloro-5,6 dicyanobenzoquinone based on the aldehyde to form a compound having the formula II as defined above;

c) combining a compound having the formula II with the acetate of the metal M to form a compound having the formula III *in situ* as defined above; and,

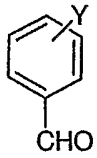
d) combining the compound having the formula III with a halogenating agent, to form a compound having the formula I.

The compound of formula II is produced *in situ* and is used directly in step d with no further isolation or purification. This process therefore provides a efficient method of synthesising a compound of formula I, while minimising the laborious and time consuming isolation and purification steps.

For the purposes of the sixth aspect of the invention, the compound having the formula (II) is preferably combined with the metal acetate in dichloromethane. Furthermore, the halogenation is preferably carried out in an aliphatic alcohol having 1 to 6 carbon atoms, preferably methanol. The insertion of the metal and the halogenation are preferably carried out at ambient temperature.

Each process described above provides for the reproducible production of enhanced levels e.g. tens of grams of the product of the process thereby allowing for scale up of the reaction in a way not previously possible and particularly allowing for the production of the products on a commercial scale.

The seventh aspect of the invention relates to a process for the formation of an aldehyde having the formula



wherein Y is as defined for a compound of formula I, comprising activation of a carborane with acetonitrile, reaction with propargyl oxybenzyl acetate to form an alcohol and subsequent oxidation. Preferalby the carborane is decaborane.

For the avoidance of doubt, the groups R, M and Y in any of compounds of formula II, III, IV or the aldehyde are defined as for a compound of formula I. Furthermore, it will be appreciated that one or more of the processes set out for

the present invention can be combined with one or more of the other process set out for the present invention to provide a process for the provision of compounds of formula I, II, III or IV as defined herein.

Brief description of the Figures

Fig. 1 shows a reaction scheme for the preparation of the substituted porphyrin 1,2,3,4,5,6,7,8-octabromo-α,β,γ,δ-tetra-[3-(1,2-dicarbododecaborane-(12)-1-yl-methoxyl)phenyl]porphynato-copper^{II} (also known as CuTCPBr).

Detailed description of the invention

A process for the preparation of a compound having the formula I as defined comprises halogenation of a compound of formula III as defined above.

The compound having the formula III is combined with a halogenating agent in a solvent solution preferably comprising an aliphatic alcohol having from 1 to 6 carbon atoms, dichloromethane, trichloromethane and/or carbon tetrachloride or, preferably a mixed solvent system such as mixture of two or more of an aliphatic alcohol having from 1 to 6 carbon atoms, dichloromethane trichloromethane, and/or carbon tetrachloride. The mixed solvent is preferably trichloromethane and carbon tetrachloride. In a particular feature of the invention, the solvent system preferably comprises dichloromethane.

The solvent system may additionally comprise a base such as an organic base. Examples of suitable bases include pyridine, alcohols etc.

Where the compound of formula III is combined with a halogenating agent in an aliphatic alcohol, the aliphatic alcohol has from 1 to 6 carbon atoms,

preferably 1 to 4 carbons atoms. The aliphatic alcohol can be one or more of methanol, ethanol, propanol, butanol, pentanol or hexanol. Preferably the aliphatic alcohol is methanol. It will be appreciated that when the halogenation is carried out in an aliphatic alcohol, it is not necessary to use an organic base such as pyridine.

The halogen represented by R may be F, Cl, Br, I, preferably Br.

Examples of suitable halogenating agents are F_2, Cl_2, Br_2 and I_2. A particularly preferred halogenating agent is bromine.

As discussed above, for a compound of formula I, one or more of the groups R is a halogen, preferably two, three, four, five, six, seven or eight of the groups R are halogen, most preferably all the R groups are halogen. The halogenating agent will therefore be provided in sufficient quantity to allow the desired degree of halogenation. Preferably, sufficient halogenating agent is used to ensure that each R in formula I represents halogen. The halogenating agent will therefore be provided in sufficient excess to ensure that each R in formula I represents halogen. The halogenating agent can be provided at a level of 8 to 20 equivalents (compared to the amount of the compound of formula III), preferably at a level of 9 to 14 equivalents.

Preferably, a solution of the halogenating agent is added incrementally to a solution of the compound of formula III over a period from 1 minute to 6 hrs, preferably from 0.5hr to 3 hours and the resulting mixture stirred for a period from 10 minutes to 6 hours, preferably 1 hour to 4 hours.

The reaction may be carried out at a temperature from 0 to 80°C, preferably at ambient temperature.

Preferably, a base such as pyridine is added and the resulting mixture stirred for a period from 2 hours to 48 hours.

Where the compound of formula I is formed by combining a compound of formula III with a halogenating agent and an aliphatic alcohol having from 1 to 6 carbon atoms, the halogenating agent is preferably bromine.

It will be appreciated that any remaining halogenating agent or any reaction products of the halogenating agent should be removed from the reaction mixture after the halogenation step has been completed. This removal can be carried out using methods well known in the art. In a preferred feature of the invention, hydrogen bromide, formed during the formation of a compound of formula I, is removed using a base, preferably an inorganic base, such as one or more bicarbonate salts of a group 1A metal.

The compound of the formula III is produced by combining a compound having the formula II as defined above with the acetate of the metal M, preferably at ambient temperature, to form a compound having the formula III.

For the purposes of this invention, the metal M may be selected from the transition metals or the lanthanide metals such as vanadium (V), chromium (Cr), manganese (Mn), iron (Fe), ruthenium (Ru), technetium (Tc), chromium (Cr), platinum (Pt), lead (Pd), cobalt (Co), cadmium (Cd), nickel (Ni), copper (Cu), zinc (Zn), germanium (Ge), molybdenum (Mo), indium (In), tin (Sn), yttrium (Y), gold (Au), barium (Ba), tungsten (W), and gadolinium (Gd). The most preferred metals are Cu, Zn, Ni, Pb and Mn.

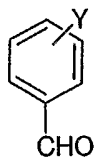
The metal acetate is preferably provided at a level of 1 to 5 equivalents (compared to the amount of compound of formula II), more preferably at a level of from 1.1 to 1.5 equivalents.

The formation of a compound of formula III is preferably carried out in a mixture of dichloromethane and methanol. The molar ratio of dichloromethane and methanol in the solvent mixture may be from 10:1 to 1:5. Alternatively, the formation of a compound of formula III can be carried out in dichloromethane. Where the compound of formula III is produced by the combination of a compound of formula II with a metal acetate in dichloromethane, the metal acetate is preferably copper acetate.

The reaction may be carried out at a temperature from 10 to 70°C, more preferably at a temperature from 15 to 60 °C, more preferably at ambient temperature.

The reaction may be carried out for a period of time from 0.01 hour to 2 hours, preferably from 0.1 hour to 0.5 hour.

The compound having the formula II as defined above may be prepared by a process comprising combining an aldehyde having the formula



wherein Y is as defined above with pyrrole in the presence of a Lewis acid catalyst to form a compound having the formula IV as defined above.

The use of pure pyrrole, preferably freshly distilled pyrrole, enhances the yield. The pyrrole is preferably at least 98% to 99.99% pure, more preferably from 99.5% to 99.99% pure.

Preferred solvents for the reaction include dichloromethane (DCM) and trichloromethane.

Suitable Lewis acid catalysts include but are not limited to trifluoroacetic acid, $ZnCl_2$, $FeCl_2$, $FeCl_3$, $AlBr_3$, $AlCl_3$, H_2SO_4, HNO_3. A preferred Lewis acid catalyst is boron trifluoride diethyl etherate.

The reaction is preferably carried out in the absence of oxygen. Preferably, a stream of dry nitrogen is passed through a mixture of the aldehyde and pyrrole in the solvent to remove all traces of oxygen before addition of the Lewis acid catalyst.

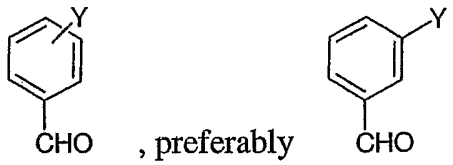
The reaction mixture may be stirred for a period of time from 5 minutes to 6 hours, preferably about 1.5 hr. The reaction is preferably carried out at ambient temperature.

Furthermore, the reaction is preferably anhydrous. Preferably, all traces of water are removed e.g. by the addition of activated molecular sieves and the resulting solution stirred for a period of time from 5 minutes to 3 hours and/or the drying of solvents, reagents and glassware before use.

The reaction mixture may then be treated with from 0.01 to 2, preferably from 0.1 to 1 molar equivalents 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) based on the aldehyde. It may be preferred to use less than 1 molar equivalent DDQ based on the aldehyde. Such quantities were found to improve the yield of

compound II. The resulting solution is preferably stirred for a period of time from 2 hours to 72 hours, preferably at ambient temperature.

The aldehyde having the formula



used in the preparation of the compound having the formula II as defined above may be prepared in several stages following the procedure described in Miura, M., et al, "Preparation of Carboranyl Porphyrins for Boron Neutron Capture Therapy", Tetrahedron Letters, 31, 2247-2250, (1990) for the purposes of this invention, Y is preferably O-CH_2-$C_2HB_{10}H_{10}$.

Alternatively the aldehyde can be produced by one or more higher yielding processes as described in the examples.

The invention further relates to the products of the processes set out above. In particular, the invention relates to a compound of formula I, II, III or V or an aldehyde as described herein as produced according to one or more of the processes set out in the invention. The compounds of the invention, particularly compounds of formula I can be used in the treatment of cancer, in particular in X-ray activated-drug therapy or photo activated drug therapy.

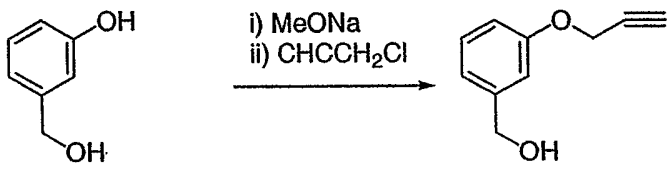
All preferred features of each of the aspects of the invention apply to all others *mutatis mutandis*.

The invention is described by way of one or more of the non-limiting examples as follows:

Example 1

All reactions were carried out under a nitrogen atmosphere in high temperature oven-dried glassware, with magnetic stirring or overhead stirrer unless otherwise stated. All intermediates and products were identified by means of proton NMR (where possible), TLC and MALDI TOF mass spectroscopy (in a dithranol matrix).

Preparation of 3-propargyloxybenzyl alcohol 3



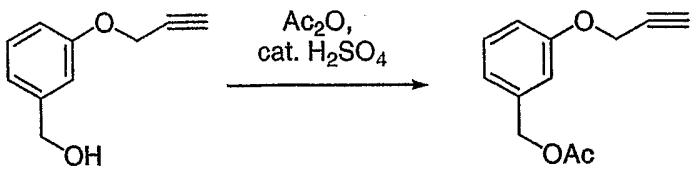
2 Fw 124
$C_7H_8O_2$

3 Fw 162
$C_{10}H_{10}O_2$

A 20.0L flange flask was charged with 3-hydroxybenzyl alcohol (97%, ex. Aldrich, 903g, 7.28mol, 1 eq.) in methanol (MeOH)(9.1L, dried over 3A molecular sieves) to give a clear solution, into which sodium methoxide (25% in methanol, ex. Aldrich, 1.746L, 7.63mol, 1.05 eq.) was slowly added with vigorous stirring. After stirring for 10min. the propargyl chloride (70wt% in toluene, ex. Aldrich, 542.6g, 805ml, 7.29mol, 1 eq) was added slowly with vigorous stirring over a period of 30 minutes. The reaction mixture was heated under reflux for 40h (isomantle set to 76°C with an internal temp. of 64°C). TLC-examination (10% MeOH in DCM) showed that the reaction was not complete. The reaction was nevertheless worked-up at this stage. The MeOH was removed by rotary evaporation, and the residue dissolved in DCM (10.2L)

to give a clear solution, which was washed with water (5.82L x 3), and dried over sodium sulfate. The solvent was removed in vacuo, to give the title compound (706g, 60%) as an orange gum.

Preparation of 3-propargyloxybenzyl acetate 4



3 Fw 162
$C_{10}H_{10}O_2$

4 Fw 204
$C_{12}H_{12}O_3$

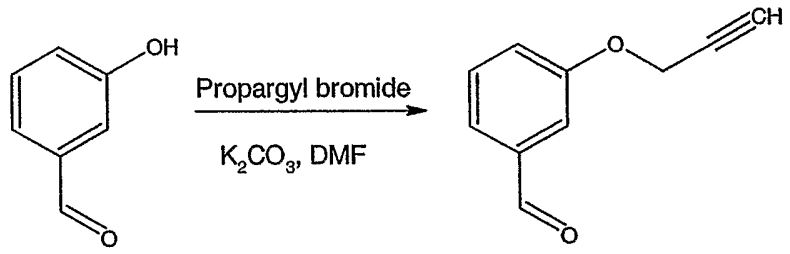
The starting material for this step was the crude material described above, containing the propargyloxy material 3 and some of the hydroxybenzyl alcohol 2.

A 5.0L flange flask was charged with 3 (706g, approx. 4.36mol, 1 eq) and acetic anhydride (99.5%, ex. Fisher, 1300ml, 1mol) to give a clear solution. Sulfuric acid (conc. 98%, 150 drops, ~3ml, catalytic) was then added very slowly (dropwise) over 30minutes, with cooling to 0°C by aid of an ice/water bath to control the exotherm to give a very dark reaction mixture. Maximum internal temperature observed was 45°C. After the addition the reaction mixture was stirred for 30min, then the reaction mixture was stirred at 99°C for 3h. TLC-examination (silica-gel plate, DCM eluent, PMA stain) showed that all the starting material had been consumed. The mixture was cooled to room temperature (r.t.) overnight to give a dark green solution, which was poured onto an ice-water mixture (2.5L water and 2.5Kg of ice) with vigorous stirring. The product was extracted with DCM (5.0L x 3), and the combined extracts washed with water (3.0L x 3), dried over Na_2SO_4, and evaporated to give a black/brown oily residue.

The crude product was purified by vacuum distillation to give the title compound 4 (598g, 67%; 40% combined yield for both steps from 2) as a colourless oil; bp. = 92-80°C/0.1-0.05 mmHg (oil-bath 127-140°C).

A compound of formula (4) can be prepared by the improved procedure documented below. This alternative procedure allows the production of (4) and subsequent compounds derived therefrom in a higher yield and a more cost effective manner.

1) Acetylation with Propargyl Bromide



Mol Wt 122 Mol Wt 160.04

1 2

The reaction was carried out in a 6L reactor, with overhead stirring.

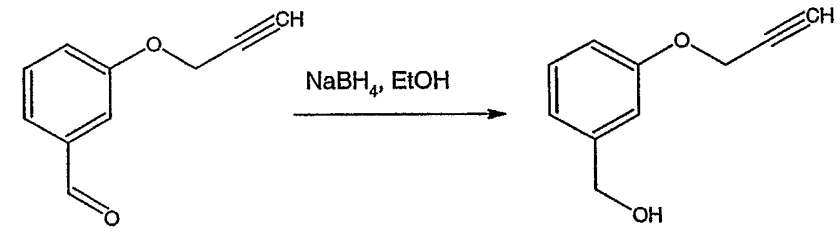
The reactor was charged with 3-hydroxybenzaldehyde (1) (500g, 4.09M) and the external temperature set to 50 °C. DMF (2 L) was added, and the solution stirred. Potassium Carbonate (848 g, 6.14M) was added in portions monitoring for any possible exotherm. (T_{max} 57 °C), the solution turning bright yellow. Propargyl bromide (550 ml, 80 wt % in toluene) was added dropwise over 1.5 hours. A mild exotherm was observed (T_{max} 57 °C).

When the addition was complete, the temperature was increased to 60 °C for 1 hr, the reaction turning to a light brown suspension. After cooling to 25 °C,

water was added (5 L), and the product extracted with toluene (3 L). The organic phase was washed with water (2 x 2L) to remove residual DMF. After separation, the solvent removed in vacuo to give an orange oil which was used without further purification.

The distilled product gradually crystallises on standing (mpt <35 °C).

2) Reduction with Sodium Borohydride



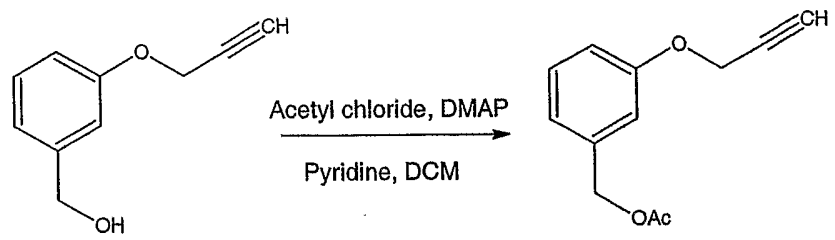
Mol Wt 160.04 Mol Wt 162

2 3

The reaction was carried out in a 6L reactor, with overhead stirring.

The reactor was cooled to –5 °C, and compound (2) was added in 1 L of ethanol then made up to 3 L with ethanol. Sodium borohydride (50 g) was added in approx. 4 g portions, (T_{max} 35 °C) with good stirring. After 30 mins more tlc analysis indicated all starting material has been consumed. The ethanol was removed in vacuo and the residual orange oil dissolved in water (3 L). 140 ml concHCl was added slowly with stirring. The aqueous layer was extracted with 2 x 1.5 L of dichloromethane, which was dried over $MgSO_4$, and used in the next step without any further purification.

3) Reaction with Acetyl chloride



Mol Wt 162 Mol Wt 204

3 4

The reaction was carried out in a 6L reactor with overhead stirring.

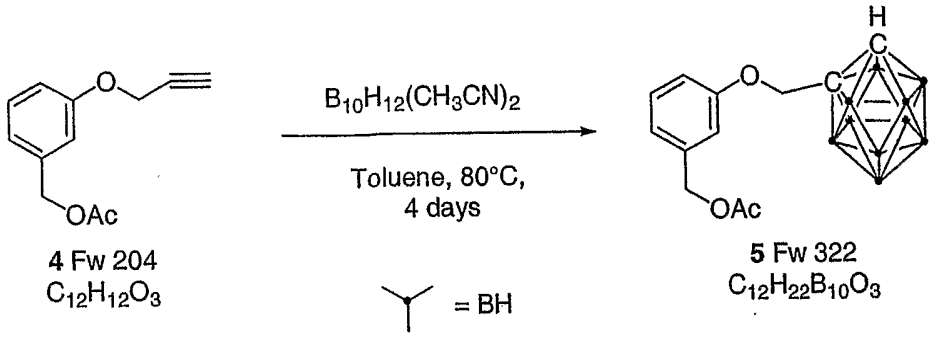
The reactor was charged with the solution of (3) (4.09 moles) in DCM (3L) from the previous step and cooled to 5 °C. Pyridine (500 ml) and DMAP (1 g) was added. Acetyl chloride (365 ml) was then added dropwise so that the internal temperature did not rise above 40 °C. When the addition was complete, the reaction was allowed to stir at room temperature for 1.5 hours. Aqueous hydrochloric acid (2N), (200 ml) was added, the reaction stirred and phases separated. The organic layer was washed with 1L of aqueous potassium carbonate (10 wt %) then with 1L of brine. The organic extracts were dried over $MgSO_4$, and the solvent removed in vacuo to give and orange oil.

The reaction was repeated 3 times and the products combined. The oil was purified by distillation in portions (0.5 mm Hg, 130 °C) to give (4) as a pale yellow oil (2.4 kg).

Preparation of 3-(o-closo-carboranylmethoxy)benzyl acetate 5

$$B_{10}H_{14} + CH_3CN \xrightarrow[\text{r.t., 3h}]{\text{Toluene}} B_{10}H_{12}(CH_3CN)_2$$

In this reaction step, the decaborane starting material is first reacted with acetonitrile to give the $B_{10}H_{12}(CH_3CN)_2$ reactive intermediate.



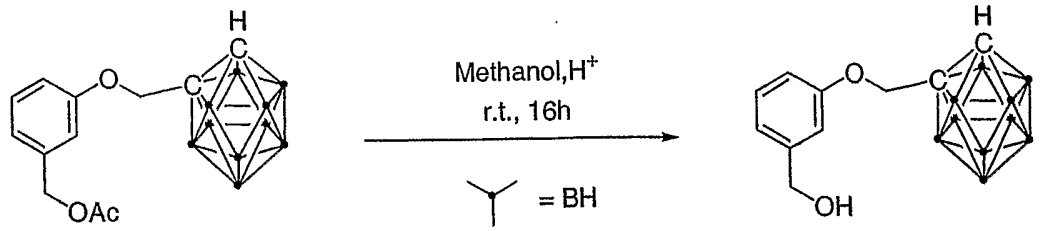
4 Fw 204
$C_{12}H_{12}O_3$

5 Fw 322
$C_{12}H_{22}B_{10}O_3$

The second stage of this step involves reaction of the activated borane with the alkyne functionality of 4 to give the desired o-closo-carborane sub-unit.

A 10.0L flange flask was charged with decaborane ($B_{10}H_{14}$, ex. Katchem, 150g, 1.23 mol, 1 eq), and anhydrous toluene (4.5L) to give a clear colourless solution. Acetonitrile (ex. Aldrich, anhydrous, 150ml) was added and the resulting mixture stirred at room temperature for 3-4h under nitrogen. The reaction was monitored for hydrogen evolution before proceeding. After hydrogen had stopped evolving, freshly distilled 3-propargyloxybenzyl acetate 4 (251g, 1.23mol, 1 eq) was added, and the resulting solution stirred at 80°C for 3-4 days; the reaction solution becoming slightly yellow. TLC-examination at this time (silica, DCM, PMA or UV developing) showed that almost all of the alkyne 4 had been consumed. The mixture was cooled to room temperature and 2.61L of a mixture of concentrated HCl (26ml), water (500ml), acetone (515ml) and methanol (1575ml) were slowly added with aid of an ice/ water bath for controlling the possible exotherm, and the resulting two-phase system stirred at room temperature for 16h to completely destroy any excess decaborane reagent. The toluene layer was separated, the aqueous layer further extracted with toluene (500ml) and the combined organics evaporated to dryness by rotary evaporation at 40°C/40mmHg. Removal of the solvent under reduced pressure gave the crude product 5 (307.0g, 77%), which was used for the next step without further purification.

Preparation of 3-(o-closo-carboranylmethoxy)benzyl alcohol 6



5 Fw 322
$C_{12}H_{22}B_{10}O_3$

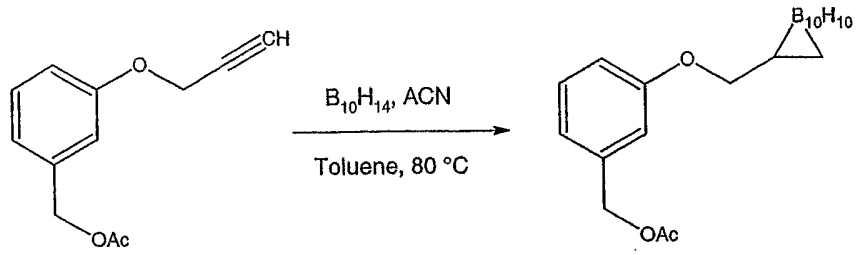
6 Fw 280
$C_{10}H_{20}B_{10}O_2$

This reaction step was again quite straightforward. The o-closo-carboranylmethoxyl groups in the starting material 5 and the product 6 were stable to the acidic reaction conditions.

Concentrated hydrochloric acid (50.0ml) was added dropwise, with stirring, to an ice-cold solution of acetate 5 (307.0g, 0.953mol, 1 eq) in methanol (3.5L), and the resulting orange solution was stirred at room temperature for 24h until TLC-examination (Silica, DCM, UV or PMA develop) showed that all of the starting material 5 had been consumed. The solvent was removed by rotary evaporation at 40°C/40mmHg, and the residue purified by column chromatography on silica gel (1.7Kg silica, 1:1 DCM/isohexane eluent) to give the alcohol 6 (205.2g, 77% yield).

An alternative process to compound 6 is outlined below:

4) Introduction of boron cage



Mol wt 204

4

Mol wt 322

5

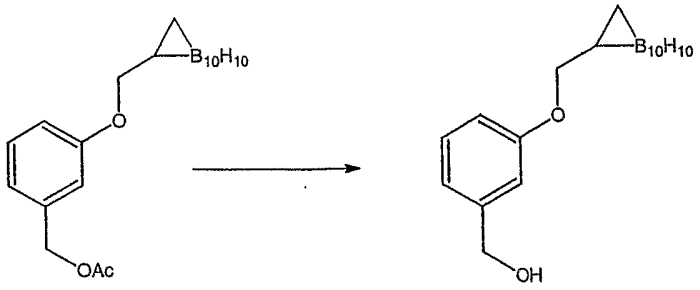
[NB: All solvents used in this step were first dried by standing over molecular sieves]

A 5L 3 necked flash was charged with 1.7L of toluene, and flushed with Nitrogen. Decaborane (200 g) was added under a nitrogen atmosphere. Acetonitrile (200 ml) was added to the reaction and it was heated over 40 mins to approximately 80 °C and maintained at this temperature for 1 hour. Hydrogen evolution was observed, as was the formation of a solid (probably the decaborane:acetonitrile complex forming).

The reaction was removed from the heat. The acetate (4) (334.7 g) was dissolved in toluene (200 ml), and half of the solution added to the stirring decaborane complex. Stirring was continued as the solid was allowed to dissolve. After an initial cooling to 76 °C, an exotherm to 81 °C was observed. The rest of the acetate solution was added and heating resumed. 100ml toluene was used to wash residual acetate into the reaction vessel. Heating was continued for 43h after which time no starting material remained. The reaction was allowed to cool and the solvent removed in vacuo to give the crude product as an orange oil (655 g).

This was used directly in the next reaction.

5) Removal of the acetyl group



Compound 6

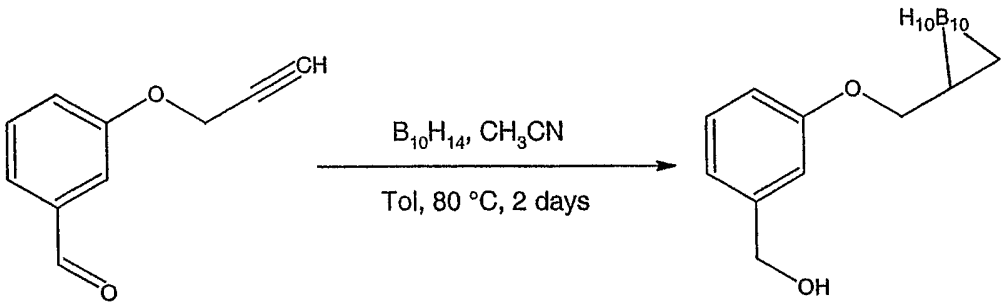
The crude product from the previous stage was dissolved in 2.5L of methanol and stirred at room temperature (25 °C), monitoring the evolution of hydrogen gas. When no further gas evolution was seen (2-3h) the reaction was cooled in an ice bath and conc. HCl (65 ml) was carefully added. A temperature increase to 30 °C was observed. After 4 hours the reaction was shown to be almost complete by tlc. Stirring was continued overnight.

After 24 hours the methanol was removed in vacuo at 30 °C. When approximately 2 L of methanol had been removed, toluene (1 L) was added and the residual methanol removed. The solution was filtered through silica and the silica washed with dichloromethane until all the product was isolated (tlc analysis).

Solvent was removed and the crude material purified by chromatography using dichloromethane as solvent. Yield of purified product, 204g plus approximately 50g mixed fractions which chromatographed with other mixed material.

Compound 6 can also be prepared by the process outlined below. The process allows a more direct synthesis of the compounds of the invention. This process

involves the direct addition of the borane cage onto an aldehyde as illustrated below.



Decaborane (50g) is dissolved in toluene (450ml) under nitrogen. Acetonitrile (50ml) is added and the mixture heated at 80 °C for 3h. The aldehyde (64g) in toluene (50ml) is added and the mixture heated for 40h (no starting material). The solvent is removed under vacuum and the residue heated at reflux in methanol for 8h to destroy borane residues. Solvent is removed and the product isolated by chromatography using dichloromethane as solvent.

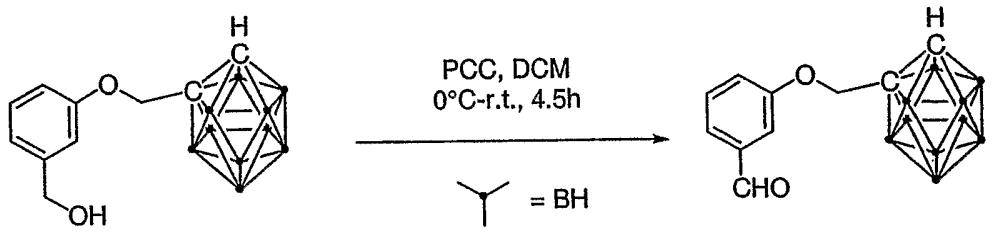
Fraction 1	9.3g, contaminated with higher R_f borane residues
Fraction 2	56.7g, main fraction
Fraction 3	2.3g, contaminated with lower R_f borane residues

The product is shown to be identical by HPLC to the product generated by alternative procedures.

Decaborane (2.25g) is heated at reflux in 15ml HPLC grade acetonitrile for 3h (suspended solid). Compound 4 (3.7g) in acetonitrile (10ml) is added. The mixture is heated for 8h (complete consumption of starting material), cooled, and the solvent removed. The residue is dissolved in dichloromethane and filtered through silica, washing with about 100ml dichloromethane.
The solvent is removed to give 4.2g of the crude product.

The use of acetonitrile has resulted in an acceleration of the reaction between decaborane and compound 4. This acceleration was unexpected and provides a significant benefit and advancement in the production of compounds of the invention.

Preparation of 3-(o-closo-carboranylmethoxy)benzaldehyde 7



6 Fw 280
$C_{10}H_{20}B_{10}O_2$

7 Fw 278
$C_{10}H_{18}B_{10}O_2$

This was a relatively routine step, and the yield of the product aldehyde 7 was quite high (~90%). A significant factor in this step was that it was necessary to carry out the oxidation under strictly anhydrous conditions or else it failed.

A solution of alcohol 6 (205.0g, 0.732mol, 1 eq) in dry DCM (1.5L) was added dropwise to an ice-cooled suspension of pyridinium chlorochromate (PCC, 244.6g, 1.135mol, 1.55 eq) in dry DCM (750ml), and the resulting mixture stirred at room temperature for 4.5h. TLC-examination showed (silica, DCM, UV or PMA develop) that all of the alcohol 6 had been consumed. The mixture was filtered through a pad of silica gel (1.5kg of silica), and the filter cake was washed with DCM. The filtrate was then evaporated to dryness to give the product 7 (187g, 92% yield) as a colourless solid.

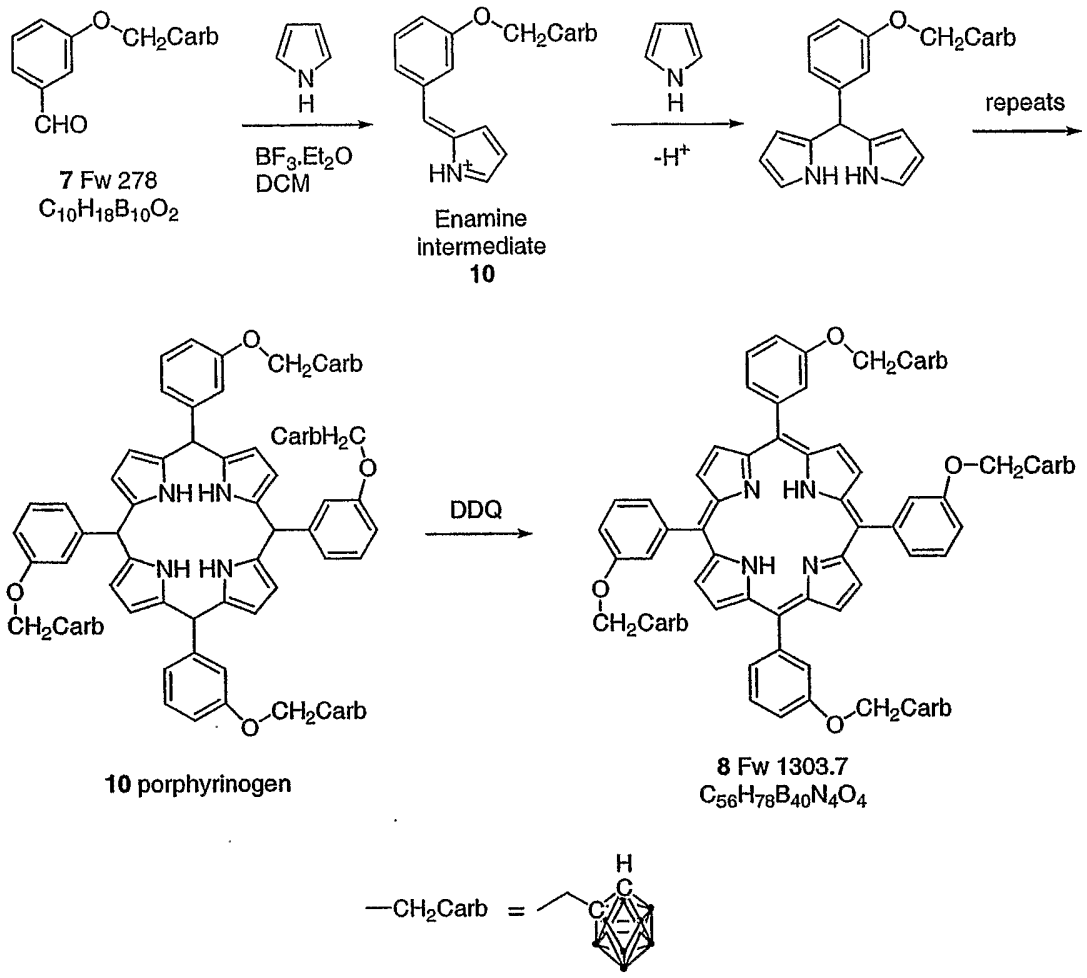
An alternative and higher yielding synthesis of compound 7, which avoids the need for oxidation, is outlined below:

Step A

Decaborane (12.2g, 0.1 mole) is heated at reflux in 50ml acetonitrile for 5h. The volume of solvent is reduced to about 50% and replaced with 75ml dry toluene. Propargyl acetate (19.8g, 0.2 mole) is added and the mixture heated at 80-90°C for 36h. Solvents and excess reagent are removed by rotary evaporation. The residue is dissolved in 50ml methanol and 5ml conc. HCl is added. After leaving overnight, the solvent is reduced to low volume, toluene (100ml) added and the toluene solution washed with 10% potassium carbonate. After removal of the solvent, the residue is dissolved in a small volume of dichloromethane and passed through a short plug of silica, eluting with dichloromethane. After removal of the solvent, 12.9g product is obtained.

The alcohol is dissolved in dichloromethane (60ml). Pyridine (12ml, 2eq) is added and the mixture cooled to 0-5°C. Methanesulphonyl chloride (7.1ml, 1.25eq) is added and the mixture stirred for 5 hours then 1h at room temperature. The reaction is quenched with 100ml 2M HCl, the layers separated and the organic layer washed with water and dried. After removal of the solvent, the crude residue is treated with 3-hydroxybenzaldehyde (12.2g, 1.3eq), potassium carbonate (20g) in DMF (60ml) at 90-100°C for 8h. The mixture is poured onto water (250ml) and extracted with toluene (100ml then 50ml). The combined toluene extracts are washed with 50ml 10% potassium carbonate solution then water and dried. Evaporation of the solvent affords compound 7 (18.9g). The compound can be purified further by recrystallisation from diisopropyl ether if required.

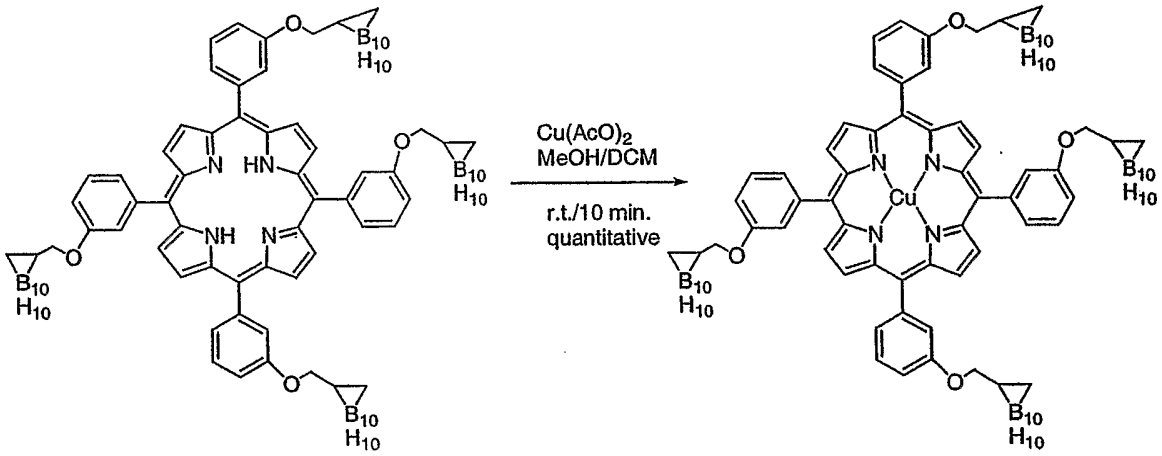
<u>Preparation of (α,β,γ,δ-tetra-[3-(1,2-dicarbododecaborane (12)-1-ylmethoxyl)-phenyl] porphyrin 8</u>



A 10L flange flask equipped with an overhead stirrer and a nitrogen inlet/outlet, was charged with aldehyde 7 (163g, 0.586 mol. 1eq), dry DCM (8.0L) and freshly distilled pyrrole (39.26g, 0.586mol, 1eq) and a stream of dry nitrogen bubbled through the reaction mixture for 24min to remove all traces of oxygen. Boron trifluoride diethyl etherate (3.52ml) was added, and the resulting solution stirred at room temperature for 1.5h, taking on a red/brown colouration. TLC (silica, 1:1 DCM / isohexane) showed that all 7 had been consumed. Activated 4A molecular sieves (106g) were added to remove all traces of water and the resulting solution stirred for 30min. The reaction mixture was then treated with 2,3-dichloro-5,6-dicyanobenzo-quinone (DDQ, 101g, 0.44mol, 0.76eq) and stirred at room temperature for 20h. The reaction

mixture was filtered to remove the sieves and the product was loaded onto a silica-gel column (1.0Kg silica, 1:1 DCM/isohexane to 100% DCM gradient). As the elution was carried out the crude material precipitated out on the column and so it was necessary to extract/wash the product off the silica gel using methanol (6 x 10.0L). The product was isolated by filtering and concentrating the methanolic extracts/washes, which gave 60.9g (32% yield) of the slightly impure porphyrin 8. This material was combined with the product from a pilot reaction to give 71.4g of the porphyrin 8.

Preparation of α,β,γ,δ-tetra-[3-(1,2-dicarbododecaborane (12)-1-ylmethoxyl] phenyl]-porphorynato-copper(II) 9



8 Fw 1303
$C_{56}H_{78}B_{40}N_4O_4$

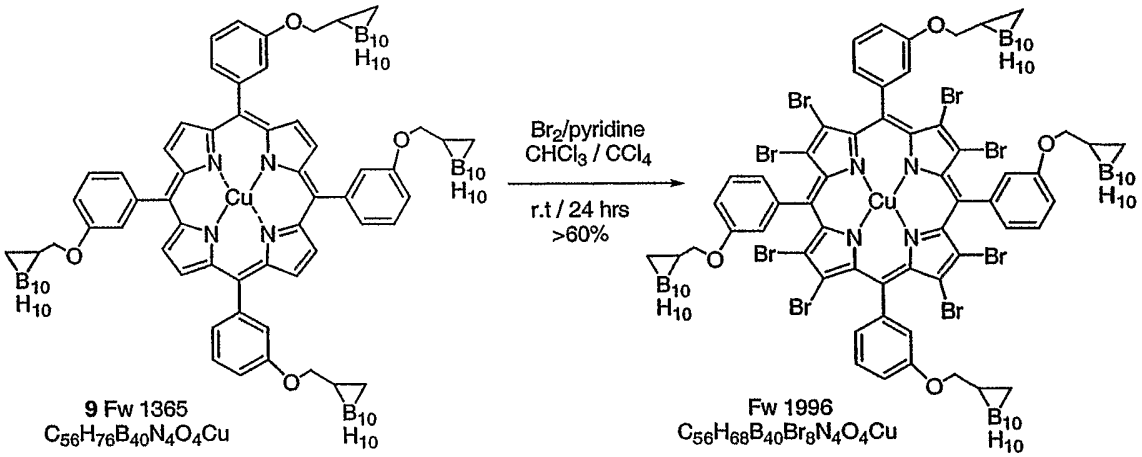
9 Fw 1365
$C_{56}H_{76}B_{40}N_4O_4Cu$

The cupration reaction proceeded smoothly at room temperature in a DCM and methanol mixed solvent system in almost quantitative yield.

Copper(II) acetate (55.6g) was mixed with dry methanol (5.54 L) and the mixture heated to 50°C for 20h, resulting in a clear, blue-coloured solution, which was cooled to room temperature then added to a stirred, dark purple

coloured, solution of porphyrin 8 (71.4g, 54.79mmol) in DCM (2.79L). The reaction mixture was stirred at room temperature for 10min, taking on a dark red colouration, after which TLC (silica, 1:1 DCM/isohexane) showed complete consumption of 8. The dark red solution was concentrated to half volume on a rotary evaporator at 30°C/40mmHg, then diluted with DCM (2.0L). The resulting solution was passed through a pad of silica-gel (2 x 1.5kg), which was washed with DCM to give a solution of 9. The solvents were evaporated to give 64.6g (86% yield) of 9.

Preparation of 1,2,3,4,5,6,7,8-octabromo-α,β,γ,δ-tetra-[3- (1,2-dicarbododecaborane (12)-1-ylmethoxyl)phenyl]porphynato-copper(II)



A solution of bromine (229g, 73.5ml, 1.43mol) in a mixture of carbon tetrachloride and dry chloroform (1.2L each) was added dropwise, at room temperature, over 1h to a stirred solution of porphyrin 9 (64.6g, 47.32mmol) in chloroform /CCl_4 (6.0L each) and the resulting solution stirred for 4h. Pyridine (193ml, 188.5g, 2.38mol) was added and the resulting mixture stirred at room temperature for a further 20h. TLC (silica, 1:1 DCM/isohexane) showed that all of the starting material had been consumed. A 20% aqueous solution of

$Na_2S_2O_5$ (2.7L) was then added, and the mixture stirred vigorously for ~10min to destroy any excess bromine. The mixture was diluted with water (2.7L), the stirring continued for 10min, and the organic and aqueous phases separated. The organic phase was washed with water (2.7L), dried over sodium sulfate, filtered, and the solvents evaporated at 30°C/40mmHg to give a dark coloured residue. This was purified by passing through a pad of silica (1.3Kg) (1:1 DCM/isohexane eluent) to give 10 (71g, 75%) as a very dark green solid. Mass spectrum (MALDI-TOF LD^+ in dithranol) analysis showed the expected molecular ion pattern.

Production of a compound of formula I using the one-pot procedure

The following example is provided as a non-limiting example of the above procedure:

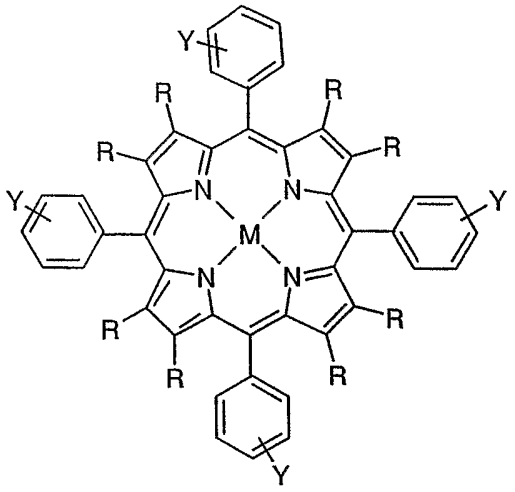
Finely powdered copper acetate, 130mg (1.4 equivalents) and (α,ß,λ,δ-tetra-[3-(1,2-dicarbododecaborane (12)-1-ylmethoxyl)phenyl] porphyrin, 0.65g (0.5 mmole) are rapidly stirred in dichloromethane (23ml) for approximately 2 hours, or until complete by HPLC analysis. To this is added 3.6ml of a freshly prepared 10% solution of bromine in HPLC grade methanol (14 eq) with the temperature at about 20 °C. The mixture gradually darkens as PP 200 forms. After about 8h, the reaction is shown to be complete by HPLC analysis. Sodium bicarbonate (2.5g) is added and the mixture stirred for 10 minutes. The mixture is filtered through a pad of celite, which is washed with dichloromethane (50ml).

The solvents plus excess bromine are removed, keeping the temperature below 30 °C. The residue is dissolved in a minimum volume of dichloromethane and purified by passing through a pad of silica eluting with dichloromethane. After

removal of solvent and high vacuum treatment, 0.95 grams of product is obtained which is of a similar purity to previously described procedures.

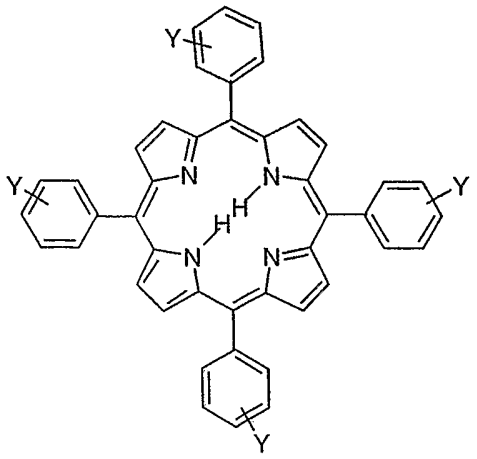
Claims

1. A process for the preparation of a compound having the formula I



I

wherein M is a single-photon-emission tomography imageable radiometal and/or a paramagnetic metal, R is hydrogen or a halogen provided that at least one R is halogen and Y is selected from ortho, meta or para $O(CH_2)_nC_2HB_9H_{10}$ or $O(CH_2)_nC_2HB_{10}H_{10}$ wherein n is 0 or an integer from 1 to 20 and $O(CH_2)_nC_2HB_9H_{10}$ is nido ortho-, meta- or para-carborane and $O(CH_2)_nC_2HB_{10}H_{10}$ is ortho-, meta- or para-carborane, said process comprising: combining a compound having the formula III



with a halogenating agent to form a compound having the formula I.

2. A process for the preparation of a compound having the formula I as defined in claim 1, said process comprising:
combining the compound having the formula III with a halogenating agent in an aliphatic alcohol having from 1 to 6 carbon atoms.

3. A process as claimed in claim 2 wherein the aliphatic alcohol is methanol.

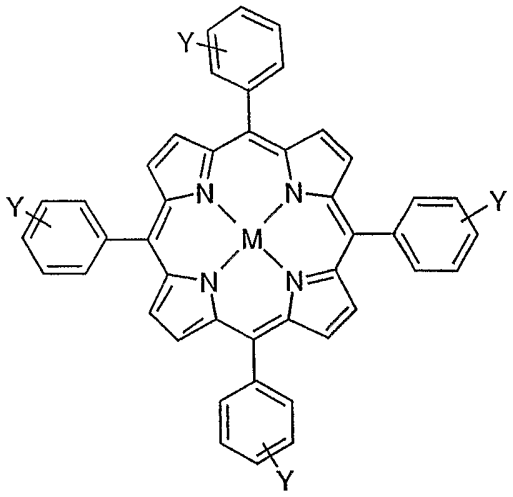
4. A process for the preparation of a compound of formula I as defined in claim 1, said process comprising combining the compound having the formula III with a halogenating agent in trichloromethane and carbon tetrachloride solvent system.

5. A process according to any one of claims 1 to 3 wherein the metal is Cu.

6. A process according to any one of claims 1 to 5 wherein the halogenating agent is bromine.

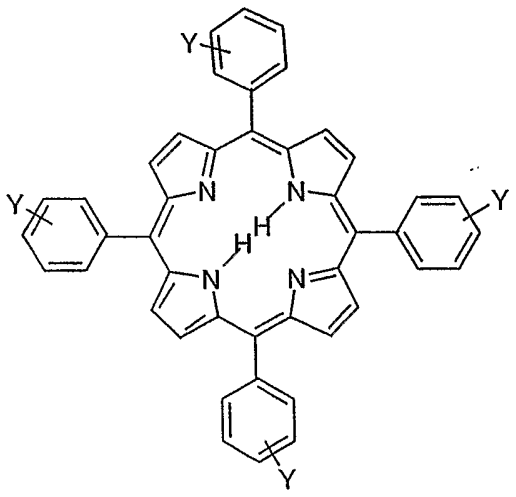
7. A process as claimed in claims 1 to 6 wherein the halogenating agent is provided at a level of 8 to 20 equivalents.

8. A process for the preparation of a compound having the formula III



III

wherein M is a single-photon-emission tomography imageable radiometal and/or a paramagnetic metal and Y is selected from ortho, meta or para $O(CH_2)_nC_2HB_9H_{10}$ or $O(CH_2)_nC_2HB_{10}H_{10}$ wherein n is 0 or an integer from 1 to 20 and $O(CH_2)_nC_2HB_9H_{10}$ is nido ortho-, meta- or para-carborane and $O(CH_2)_nC_2HB_{10}H_{10}$ is ortho-, meta- or para-carborane, said process comprising combining a compound having the formula II



II

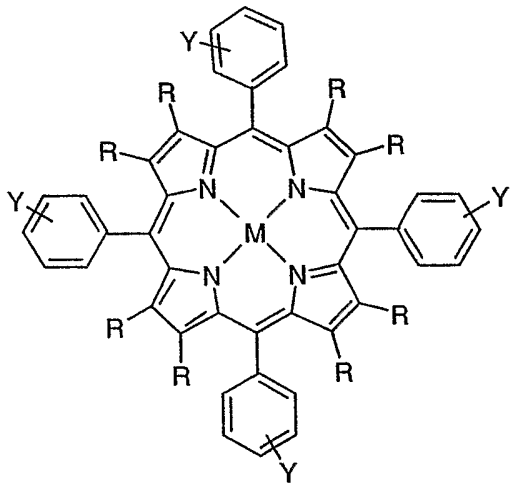
with the acetate of the metal M, to form a compound having the formula III.

9. A process for the preparation of a compound having the formula III as defined in claim 8, said process comprising:

combining a compound having the formula II with the acetate of the metal M in dichloromethane or in a mixture of dichloromethane and methanol.

10. A process as claimed in any one of claims 8 to 9 wherein the metal acetate is provided at a level of 1 to 5 equivalents.

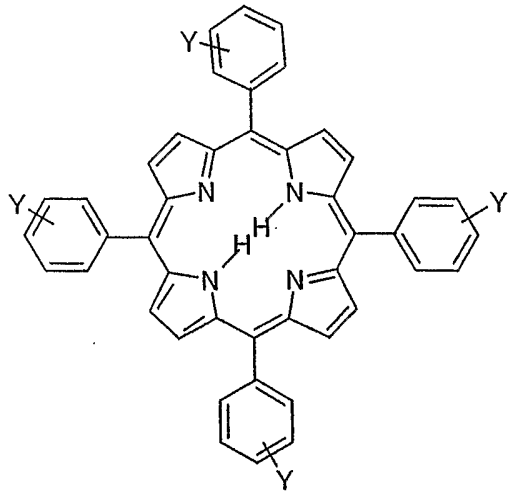
11. A process for the preparation of a compound having the formula I



I

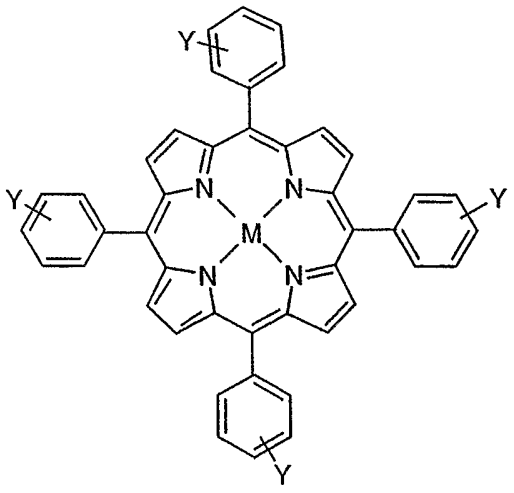
wherein M is a single-photon-emission tomography imageable radiometal and/or a paramagnetic metal, R is hydrogen or a halogen provided that at least one R is halogen and Y is selected from ortho, meta or para $O(CH_2)_nC_2HB_9H_{10}$ or $O(CH_2)_nC_2HB_{10}H_{10}$ wherein n is 0 or an integer from 1 to 20 and $O(CH_2)_nC_2HB_9H_{10}$ is nido ortho-, meta- or para-carborane and $O(CH_2)_nC_2HB_{10}H_{10}$ is ortho-, meta- or para-carborane, said process comprising:

a) combining a compound having the formula II



II

with the acetate of the metal M to form a compound having the formula III



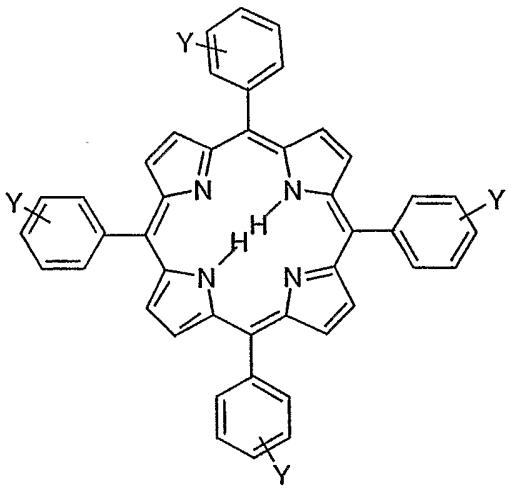
III

and;

b) combining the compound having the formula III with a halogenating agent to form a compound having the formula I.

12. A one pot process for the production of a compound of formula I comprising the *in situ* formation of a compound of formula III as claimed in any one of claims 8 to 10, followed by the halogenation of the *in situ* generated compound of formula III as claimed in any one of claims 1 to 7.

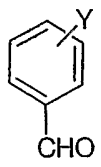
13. A process for the preparation of a compound having the formula II



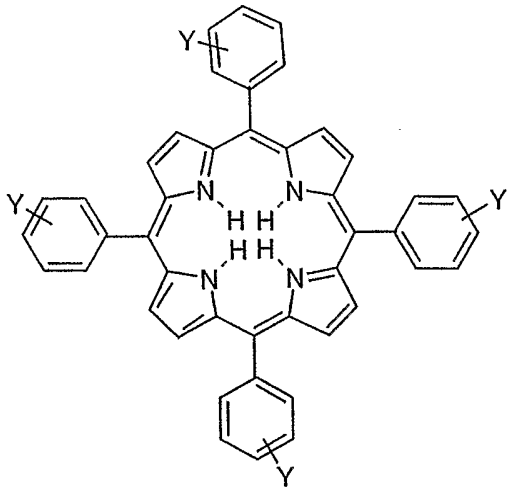
II

wherein Y is selected from ortho, meta or para $O(CH_2)_nC_2HB_9H_{10}$ or $O(CH_2)_nC_2HB_{10}H_{10}$ wherein n is 0 or an integer from 1 to 20 and $O(CH_2)_nC_2HB_9H_{10}$ is nido ortho-, meta- or para-carborane and $O(CH_2)_nC_2HB_{10}H_{10}$ is ortho-, meta- or para-carborane, said process comprising

a) combining an aldehyde having the formula



with pyrrole in the presence of a Lewis acid catalyst to form a compound having the formula IV



IV

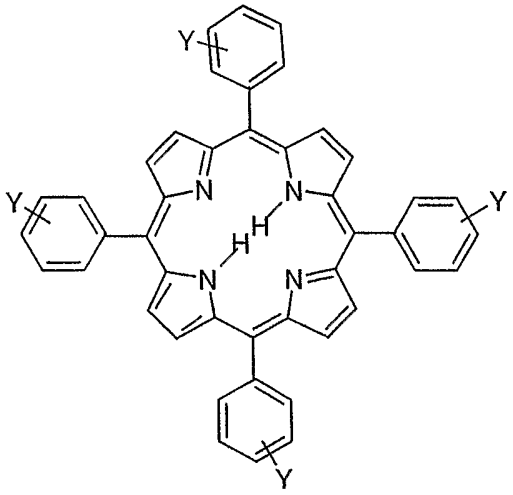
and;

b) oxidising the compound having the formula IV by the addition of from 0.1 to 1 molar equivalents 2,3-dichloro-5,6-dicyanobenzoquinone based on the aldehyde.

14. A process according to claim 13 wherein the pyrrole is at least 98% to 99.99% pure, preferably freshly distilled.

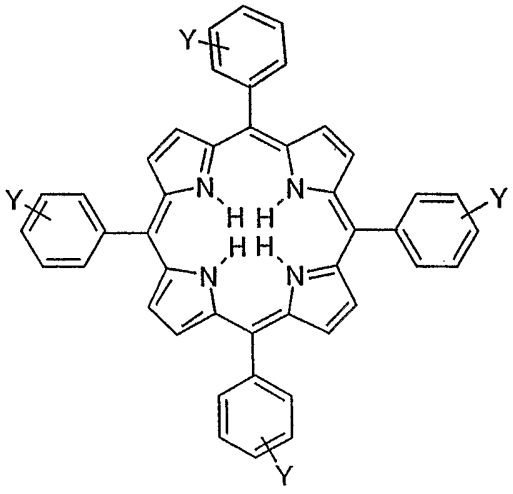
15. A process according to claim 13 or claim 14 wherein after step a) and before step b) all traces of water are removed.

16. A process for the preparation of a compound having the formula II



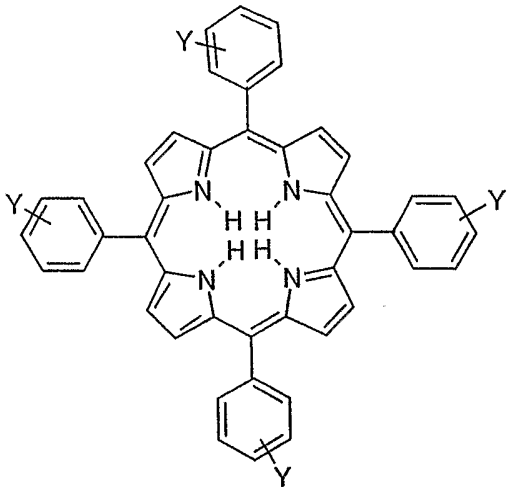
II

wherein Y is selected from ortho, meta or para $O(CH_2)_nC_2HB_9H_{10}$ or $O(CH_2)_nC_2HB_{10}H_{10}$ wherein n is 0 or an integer from 1 to 20 and $O(CH_2)_nC_2HB_9H_{10}$ is nido ortho-, meta- or para-carborane and $O(CH_2)_nC_2HB_{10}H_{10}$ is ortho-, meta- or para-carborane, said process oxidising a compound having the formula IV



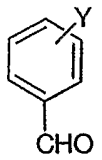
by the addition of 2,3-dichloro-5,6-dicyanobenzoquinone.

17. A process for the preparation of a compound having the formula IV



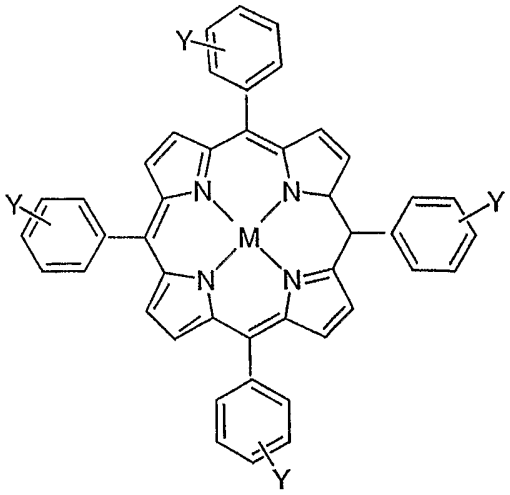
IV

wherein Y is selected from ortho, meta or para $O(CH_2)_nC_2HB_9H_{10}$ or $O(CH_2)_nC_2HB_{10}H_{10}$ wherein n is 0 or an integer from 1 to 20 and $O(CH_2)_nC_2HB_9H_{10}$ is nido ortho-, meta- or para-carborane and $O(CH_2)_nC_2HB_{10}H_{10}$ is ortho-, meta- or para-carborane, said process oxidising comprising combining an aldehyde having the formula



with pyrrole in the presence of a Lewis acid catalyst.

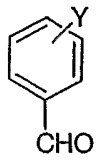
18. A process for the preparation of a compound having the formula III



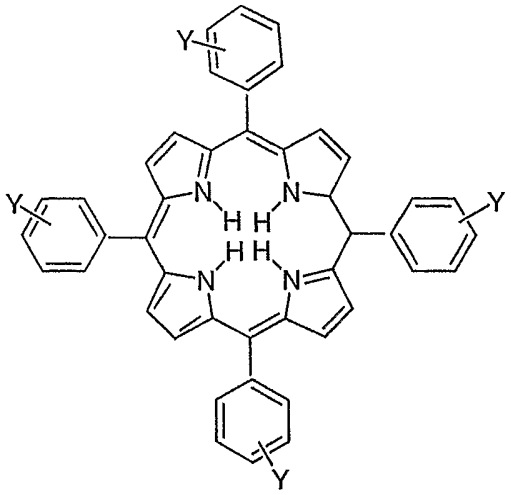
III

wherein M is a single-photon-emission tomography imageable radiometal and/or a paramagnetic metal and Y is selected from ortho, meta or para $O(CH_2)_nC_2HB_9H_{10}$ or $O(CH_2)_nC_2HB_{10}H_{10}$ wherein n is 0 or an integer from 1 to 20 and $O(CH_2)_nC_2HB_9H_{10}$ is nido ortho-, meta- or para-carborane and $O(CH_2)_nC_2HB_{10}H_{10}$ is ortho-, meta- or para-carborane, said process comprising

a) combining an aldehyde having the formula

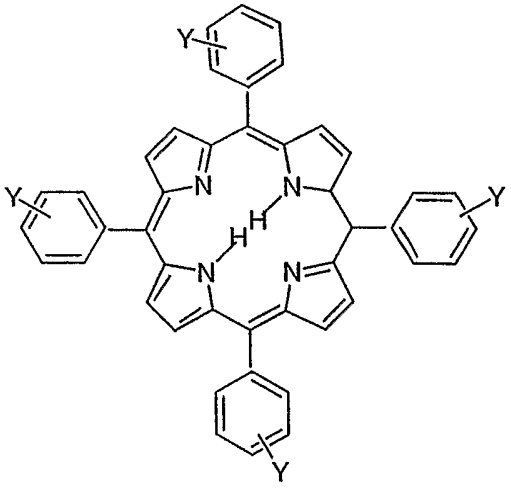


with pyrrole in the presence of a Lewis acid catalyst to form a compound having the formula IV



IV

b) oxidising the compound having the formula IV by the addition of from 0.1 to 2 molar equivalents 2,3-dichloro-5,6-dicyanobenzoquinone based on the aldehyde to form a compound having the formula II

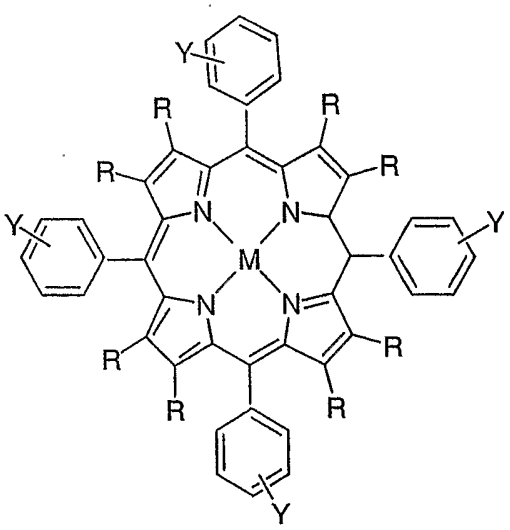


II

and,

c) combining the compound having the formula II with the acetate of the metal M, to form a compound having the formula III.

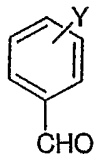
19. A process for the preparation of a compound having the formula I



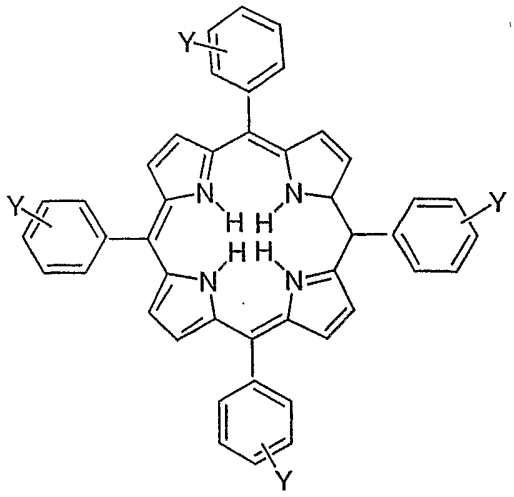
I

wherein M is a single-photon-emission tomography imageable radiometal and/or a paramagnetic metal, R is hydrogen or a halogen provided that at least one R is halogen and Y is selected from ortho, meta or para $O(CH_2)_nC_2HB_9H_{10}$ or $O(CH_2)_nC_2HB_{10}H_{10}$ wherein n is 0 or an integer from 1 to 20 and $O(CH_2)_nC_2HB_9H_{10}$ is nido ortho-, meta- or para-carborane and $O(CH_2)_nC_2HB_{10}H_{10}$ is ortho-, meta- or para-carborane, said process comprising:

a) combining an aldehyde having the formula

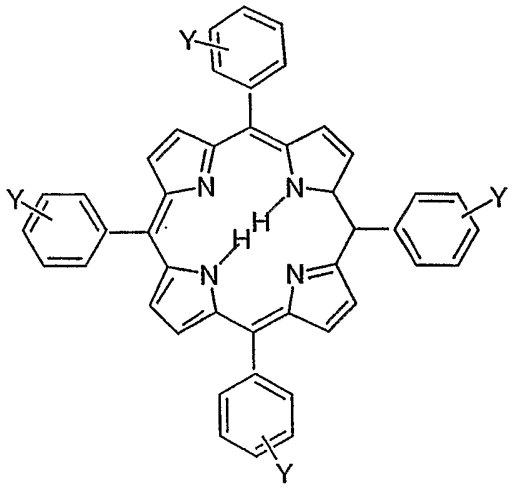


with pyrrole in the presence of a Lewis acid catalyst to form a compound having the formula IV



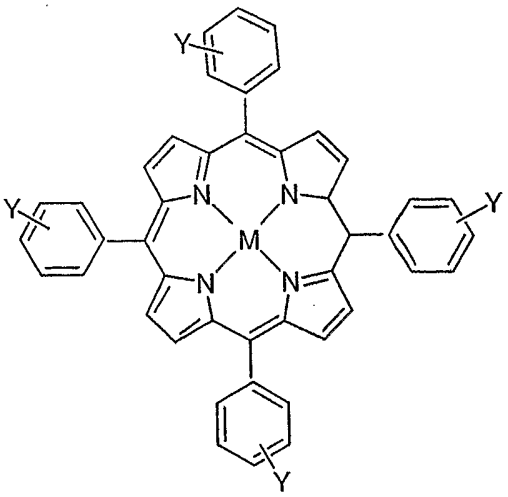
IV

b) oxidising the compound having the formula IV by the addition of from 0.1 to 2 molar equivalents 2,3-dichloro-5,6-dicyanobenzoquinone based on the aldehyde to form a compound having the formula II



II

c) combining a compound having the formula II with the acetate of the metal M to form a compound having the formula III



III

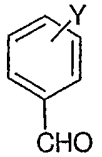
and;

d) combining the compound having the formula III with a halogenating agent in a mixed solvent solution, preferably a mixture of trichloromethane and carbon tetrachloride, preferably at ambient temperature, to form a compound having the formula I.

A process for the production of a compound of formula I as claimed in claim 19 wherein the compound of formula III as produced in step (c) is used directly to form the compound of formula I in step (d).

21. A process for the production of a compound of formula I as claimed in any one of claims 1 to 8, 11, 12, 19 and 20 wherein M is Cu, each R is bromide and Y is meta O-CH_2-$C_2HB_{10}H_{10}$.

22. A process for the formation of an aldehyde having the formula



wherein Y is as defined for a compound of formula I, comprising activation of a carborane with acetonitrile, reaction with propargyl oxybenzyl acetate to form an alcohol and subsequent oxidation.

23. A compound of formula I as produced by the process of any one of claims 1 to 8, 11, 12, 19, 20 and 21.

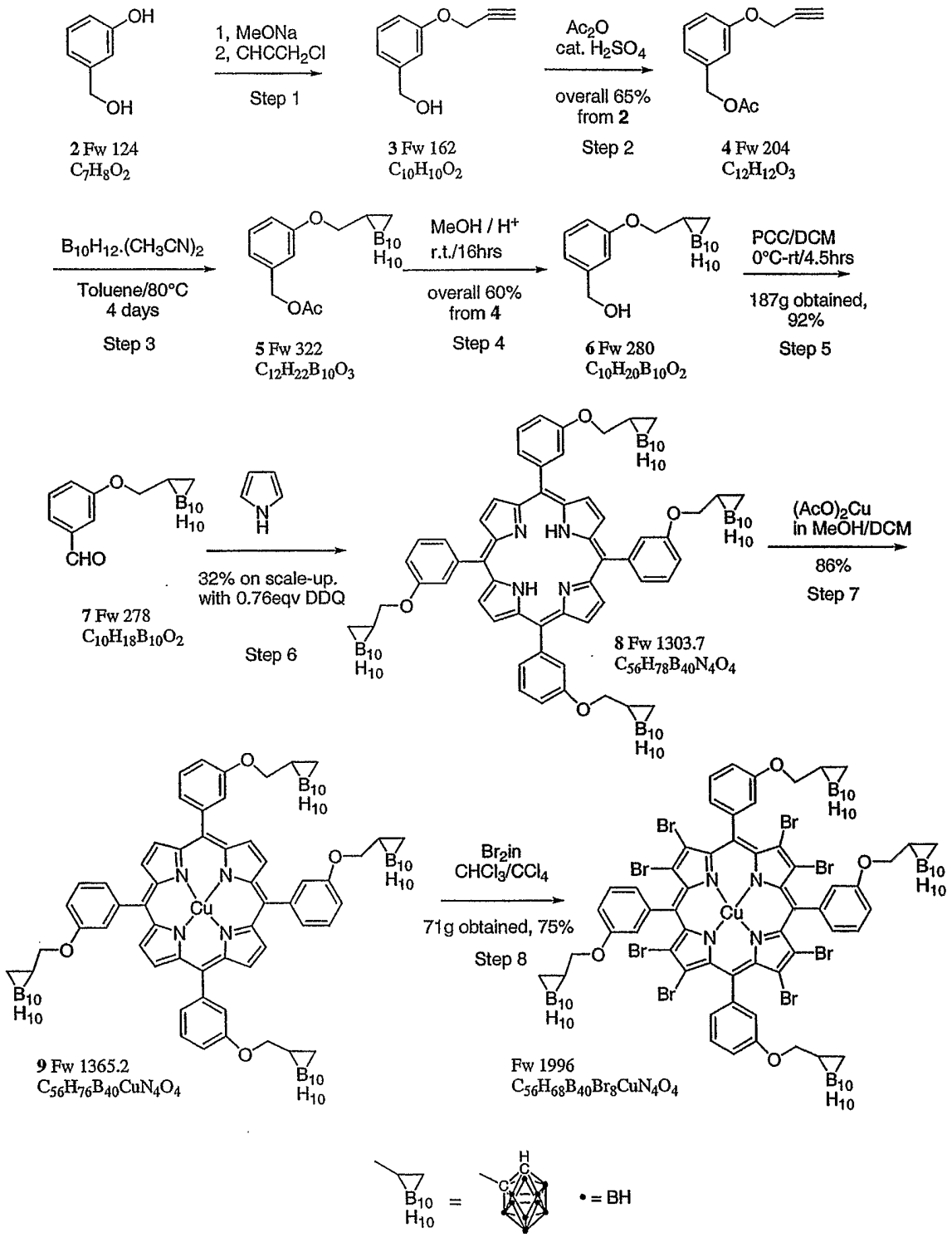

1, MeONa
2, CHCCH2Cl
Step 1
Ac2O
cat. H2SO4
overall 65%
from 2
Step 2
2 Fw 124
C7H8O2
3 Fw 162
C10H10O2
4 Fw 204
C12H12O3
B10H12.(CH3CN)2
Toluene/80°C
4 days
Step 3
MeOH / H+
r.t./16hrs
overall 60%
from 4
Step 4
PCC/DCM
0°C-rt/4.5hrs
187g obtained,
92%
Step 5
5 Fw 322
C12H22B10O3
6 Fw 280
C10H20B10O2
7 Fw 278
C10H18B10O2
32% on scale-up.
with 0.76eqv DDQ
Step 6
(AcO)2Cu
in MeOH/DCM
86%
Step 7
8 Fw 1303.7
C56H78B40N4O4
Br2in
CHCl3/CCl4
71g obtained, 75%
Step 8
9 Fw 1365.2
C56H76B40CuN4O4
Fw 1996
C56H68B40Br8CuN4O4
• = BH

FIG. 1